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# A dual role model for active Rac1 in cell migration

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**Over time we have come to appreciate that the complex regulation of Rho GTPases involves additional mechanisms beyond the activating role of RhoGEFs, the inactivating function of RhoGAPs and the sequestering activity of RhoGDIs. One class of regulatory mechanisms includes direct modifications of Rho proteins such as isoprenylation, phosphorylation and SUMOylation. Rho GTPases can also regulate each other by means of crosstalk signaling, which is again mostly mediated by GEFs, GAPs and GDIs. More complex mutual regulation ensues when and where two or more Rho proteins activate a common molecular target, i.e., share a common effector. We have recently unraveled a reciprocal mechanism wherein spatiotemporal dynamics of Rac1 activity during migration of *Dictyostelium* cells is apparently regulated by antagonizing interactions of Rac1-GTP with two distinct effectors. By monitoring specific fluorescent probes, activated Rac1 is simultaneously present at the leading edge, where it participates in Scar/WAVE-mediated actin polymerization, and at the trailing edge, where it induces formation of a DGAP1/cortexillin actin-bundling complex. Strikingly, in addition to their opposed localization, the two populations of activated Rac1 also display opposite kinetics of recruitment to the plasma membrane upon stimulation by chemoattractants. These findings with respect to Rac1 in *Dictyostelium* suggest a novel principle for regulation of Rho GTPase activity that might also play a role in other cell types and for other Rho family members.**

**Keywords:** Rac1, DGAP1, IQGAP, cortexillin, SCAR/WAVE, cell polarization, actin cytoskeleton, Rho GTPases, *Dictyostelium*

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Eukaryotic cells must establish, maintain and alter their polarity in order to efficiently migrate and orient themselves in response to external clues. Slowly moving cells such as fibroblasts and endothelial cells in culture steer predominantly by gradually changing the direction of extension of their leading edge, and it takes tens of minutes for a cell's path to deflect significantly.[1-3] Rapidly moving cells such as neutrophils and *Dictyostelium* amoebas, on the other hand, can completely reverse direction of movement within a minute or less.[4-6] Moreover, the manner in which such fast-moving cells maneuver is often quite different from their slower counterparts. These cells can turn by shutting down protrusion of the current pseudopodium and initiate extension of a new one at another position.[6] As an extreme example of this behavior, a *Dictyostelium* cell can convert its leading edge into its trailing end, and vice versa, within only 40 sec (**Fig. 1**).

The small GTPases of the Rho family represent a group of signaling proteins that are responsible for the regulation and coordination of numerous cellular activities driven by the actin cytoskeleton.[7] Early on it was recognized that prominent members of the Rho family have the capacity to trigger formation of major structures composed of filamentous actin, including stress fibers, lamellipodia and filopodia.[7,8] Since then, Rho GTPases have been shown to be essential transducers in several receptor-mediated signaling pathways, and their downstream effectors, which influence remodeling of the actin cytoskeleton, have been identified.[9,10] For a comprehensive overview of Rho GTPases-mediated signaling pathways we refer the reader to a number of excellent reviews.[7-13] Herein, we present a few selected examples of Rho effectors in mammalian cells that

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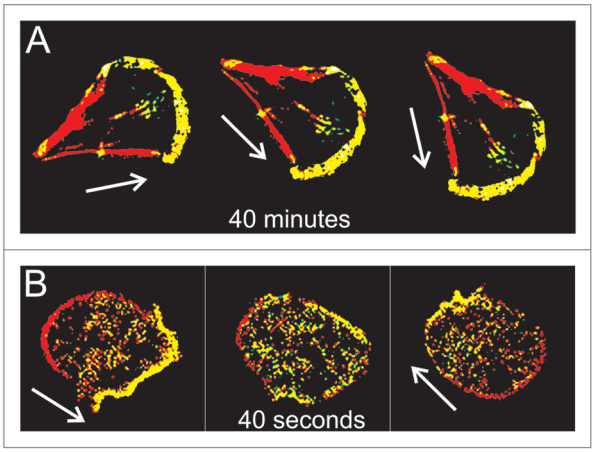


**Figure 1.** *Dictyostelium* amoebas accomplish the fastest re-polarization among eukaryotic cells. Whereas, for instance, fibroblasts typically need tens of minutes to sidetrack significantly (**A**), a *Dictyostelium* cell can turn "frontside back" within less than a minute (**B**). Cytoskeletal front and back domains are shown in yellow and red, respectively. Note that posterized pictures of cells are not to scale: fibroblasts are on average five times larger than amoebas. White arrows indicate direction of cell movement.

either bind directly to actin, or constitute an intermediate layer in signaling cascades that regulate cellular functions driven by the actin cytoskeleton.

Rho GTPases are key molecular switches regulating formation of cellular protrusions.[14] Coordinated polymerization and depolymerization of actin are both important for continuous treadmilling of the crosslinked F-actin network in a lamellipodium.[15,16] Rac and Cdc42 regulate F-actin polymerization in lamellipodia by activating the Arp2/3 complex, a process mediated through Scar/WAVE and WASP scaffolding protein complexes, respectively.[17] Similarly, indirect inactivation of the actin-depolymerizing protein cofilin is effected by Rac through the PAK/Lim-kinase pathway.[18] Cdc42 binds to and activates Diaphanous-related formins (Drfs), which are responsible for polymerization of linear actin filaments in filopodia and lamellipodia.[19,20] IQGAP proteins constitute another class of Rac and Cdc42 effectors that bind directly to F-actin, but their multiple functional roles are not yet fully understood.[21] Formation of actin-myosin II filaments has been suggested to determine the rigidity of the lateral and posterior cellular cortex, and to contribute to retraction of the tail during cell migration. Despite evidence for its interaction with Drfs,[22] the main role of Rho appears to be the regulation of actin-myosin II assembly. RhoA activates ROCK and thereby induces phosphorylation of myosin light chain (MLC), which promotes the assembly of actin-myosin II filaments.[23]

Besides relaying intracellular and extracellular signals to the actin cytoskeleton, Rho GTPases can also regulate each other by crosstalk signaling. Three modes by which these proteins can indirectly interact have been proposed: (1) mutual regulation of activity mediated largely by GEFs or GAPs; (2) regulation of expression and stability mediated by RhoGDI proteins; and (3) regulation of the same downstream pathway through a common effector.[24] An example of another signaling strategy is encountered during vulval development in *Caenorhabditis elegans*, where the small GTPase Ras switches effectors in a temporal sequence, from Raf to RalGEF, to promote divergent and mutually antagonistic cell fates.[25] In this commentary, we propose a related mechanism in *Dictyostelium discoideum*, wherein the activity of Rac1 is spatially regulated by antagonizing interactions of Rac1-GTP with two distinct effectors.

Spatially coordinated activation of different Rho GTPases is critical for polarization of migrating mammalian cells. According to the classical view, protrusion of a lamellipodium driven by actin polymerization is induced by activated Rac and Cdc42 at the front of a moving cell, whereas activated Rho regulates myosin-based retraction and detachment from the substratum at the rear.[26] A model has been proposed for the spatial segregation of these signals into antagonistic anterior and posterior signaling cascades organized by Rac/Cdc42 and Rho, respectively, which negatively regulate each other.[26] Mutual negative regulation of Rho and Rac/Cdc42, mediated by respective GEF proteins, has also been postulated in theoretical models.[27,28] Simulations based on these models result in a stable spatial distribution of Rho proteins, which resembles their experimentally determined polarized localization. Exclusive segregation of Rac and Rho into anterior and posterior domains has been challenged experimentally by the use of a FRET-based biosensor for Rac activity in neutrophils, where contrary to expectations, activated Rac was detected in the retracting tails of migrating cells.[29] Consistently, Rac1 was shown to promote RhoA-stimulated, myosin II-driven retraction of the trailing cell end.[30,31] On the other hand, it has been suggested that Rho activity is also present at the tip region of the lamellipodium in mouse cultured embryonic fibroblasts.[32] Quasi-periodical protrusions of the leading edge segments have been associated with RhoA activity, and a pacemaker cycle has been postulated that additionally involves protein kinase A and RhoGDI.[33]

Correlated fluctuations of lamellipodial segments in large cells occur on a spatial scale of ten microns and a temporal scale of a minute.[32,33] Shape fluctuations of *Dictyostelium* cells typically occur on similar spatial and temporal scales during random motility.[6] Therefore, it appears reasonable that, analogous to the situation in mammalian cells, spatiotemporal dynamics of Rho GTPase activity also correlates with, and possibly controls, dynamic cell morphology in *Dictyostelium*. In order to test this hypothesis, it is necessary to monitor dynamics of activated Rho GTPases in living amoebas. The *Dictyostelium* genome, however, lacks canonical Rho and Cdc42 family members but instead encodes 18 different Rac proteins.[34] We, therefore, decided to use fluorescent probes that interact with activated forms of 3 Rac1 isoforms in *Dictyostelium* (Rac1A, Rac1B and Rac1C),

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which share an identical effector domain with human Rac1. We used 2 such probes: a GTPase-binding domain from rat Pak1 kinase fused to a yellow fluorescent protein (GBD-YFP), and a Rac1-GTP-binding protein DGAP1 fused to a red fluorescent protein (mRFP-DGAP1). Interestingly, we found that the two Rac1 effectors were enriched at the opposite regions in the cortex of randomly migrating *Dictyostelium* cells.[35]

It is perhaps not that surprising that the two Rac1 effectors localize to different cortical regions in migrating cells. Activated Rac1 proteins interact with numerous proteins implicated in the regulation of actin dynamics and at least a half dozen have been detected in *Dictyostelium* so far: multiple IQGAP-related proteins, e.g., DGAP1[36] and GAPA,[37] Scar/WAVE,[38] formins,[39] various PAK-related kinases[40] and WASP.[41] It is remarkable, however, that the zones of GBD and DGAP1 localization are mutually exclusive, and that the dynamics of their local appearance and disappearance are exactly opposite to each other (**Fig. 2A**). Whereas such intricate spatiotemporal dynamics can be monitored in non-stimulated, randomly migrating cells, a simplified, uniform response along the cell membrane is induced in chemoattractant pulse experiments. When cAMP or folic acid are applied to competent *Dictyostelium* cells, the GBD probe is recruited to the plasma membrane (**Fig. 2B**). At the same time and with highly similar dynamics, the DGAP1 probe is released from the membrane into the cytoplasm (**Fig. 2B**). These responses are transient and last approximately 30 sec, a time interval which is comparable to the persistence time of a leading pseudopodium during random migration in *Dictyostelium*.[35]

When actin polymerization does not occur, either during spontaneous non-motile intervals or when it is inhibited by polymerization-blocking agents, the cell cortex remains labeled only with the DGAP1 probe.[35] Thus, it appears that the major fraction of active Rac1 is bound in a quaternary cortical complex that encompasses DGAP1, Rac1-GTP and the heterodimeric actin-bundling proteins cortexillin I and II.[42] In order to initiate local protrusion of a pseudopodium,

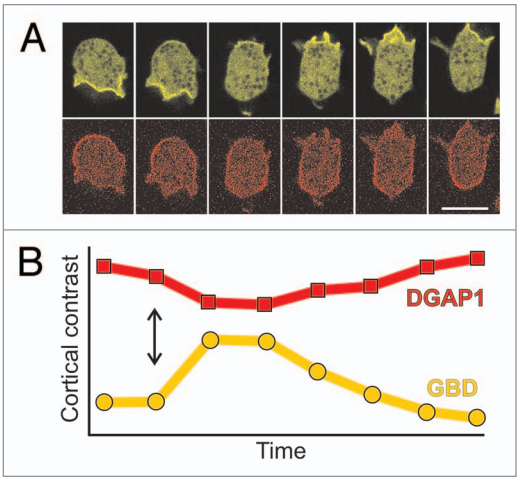


**Figure 2.** Time scales of spontaneous and induced redistributions of GBD and DGAP1 probes are comparable. (**A**) A sequence showing spontaneous re-polarization of a randomly migrating cell labeled with GBD-YFP (yellow) and mRFP-DGAP1 (red). Interval between frames, 10 sec; scale bar, 10 μm. (**B**) Response of the cortical localization of the two probes, GBD-YFP (yellow) and mRFP-DGAP1 (red), to a uniform pulse of chemoattractant. Fifty micromolars of folic acid has been applied to the cell sample at the time-point indicated by the double arrow. The cortical contrast represents the ratio between the average fluorescence intensity of a probe in the cell cortex vs. its average intensity in the cytoplasm. Interval between measurement points: 3.25 sec.

Arp2/3-mediated nucleation of branched actin filaments has to be triggered. This process is known to be activated by the pentameric Scar/WAVE complex, which resides in its passive, autoinhibited conformation until inhibition is released by binding to active Rac1 and acidic phospholipids.[43] Our results show that a local release of DGAP1 from the plasma membrane, suggesting disassembly of the quaternary complex, occurs concomitantly with recruitment of the GBD probe to the membrane, which indicates the presence of free Rac1-GTP. These results therefore suggest that the release of active Rac1 from DGAP1/cortexillin, which makes it available for binding to Scar/WAVE, is a prerequisite for initiation of Arp2/3-mediated actin assembly.

Interestingly, the scheme in which Rac1 interacts with two separate effectors at the front and at the back, which negatively regulate each other, sheds new light on results obtained more than a decade ago in a study using DGAP1-null and DGAP1-overexpressing cells.[36] DGAP1-overexpressing cells were found to have a decreased F-actin to G-actin ratio, generate fewer actin-based protrusions, and migrate at a slower speed when compared with control.[36] These findings are consistent with the notion that more Rac1 is bound to excessive DGAP1 protein in these cells and therefore not available to promote polymerization of actin and associated motility. On the other hand, DGAP1-null cells have the opposite phenotype: they contain more F-actin, make more protrusions, and move significantly faster.[36] It therefore appears that in the absence of DGAP1 more free Rac1 is available to drive actin-based motility. These mutant studies thus suggest that an appropriate balance of Rac1 effectors strongly affects the regulation of actin-based motility in *Dictyostelium* cells.

Actin treadmilling in the lamellipodium is a process characterized by the rapid turnover of its structural and regulatory elements. It has been estimated that, in *Dictyostelium*, individual actin filaments can grow at a rate of over 1,000 subunits per second.[44] Consequently, regulatory molecules that control different phases of this process, including Rac1-activated formins and the Scar/WAVE complex, have to be turned on and off at a relatively high rate, probably by binding and releasing Rac1-GTP. It is therefore tempting to speculate that individual activated Rac1 molecules are recycled at a high rate at the leading edge and hence repeatedly detected by the GBD probe. The DGAP1/cortexillin complex has a strong

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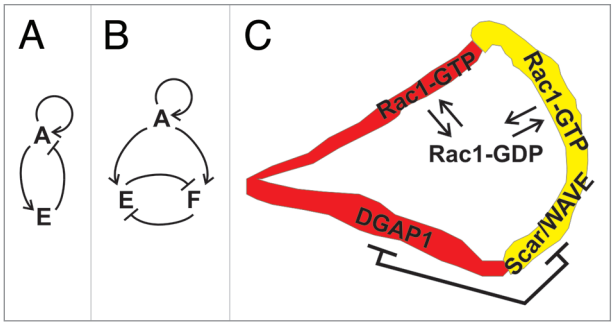


**Figure 3.** A dual role model for Rac1 in migrating *Dictyostelium* cells. (**A**) The basic circuit of an excitable network: activator A activates an effector E, which in turn inhibits A. Auto-activating activity of A is also usually incorporated in the model. (**B**) A modified version of the model wherein Rac1-GTP plays the role of an activator A that activates two effectors: the DGAP1/cortexillin complex E and the Scar/Wave complex F, which in turn mutually inhibit each other. (**C**) A schematic representation of regulation and dynamics of Rac1 in a polarized cell. Exchange between the activated form in the membrane and inactivated form in the cytoplasm is governed by the GEF-GAP-GDI-mediated mechanism in both anterior and posterior compartments. Additionally, the two major Rac1 effectors, DGAP1/cortexillin and Scar/WAVE, compete for a common pool of active Rac1 and thereby effectively act as mutual inhibitors.

influence on the viscoelastic properties of the cell cortex, harbors multiple actin-binding sites and participates in bundling of actin filaments at the lateral sides and the back of a cell.[42,45-47] This complex probably has a comparably slow disassembly rate and therefore effectively acts as a buffer for activated Rac1 in these cortical sites.[48] Locally induced disassembly of the DGAP1/cortexillin complex accompanied by the release of Rac1, analogous to its induced release in the chemoattractant pulse experiments, may serve as a trigger for initiation of a new pseudopodium. This process would soften the cortical actin layer by disrupting the crosslinked network of actin filaments beneath the plasma membrane, and simultaneously trigger formation of actin filaments orientated approximately perpendicular to the membrane, which is induced by the Rac1-Scar/WAVE-Arp2/3 pathway.[49]

Based on recent experimental observations and modeling, it has become increasingly evident that the amoeboid motility of *Dictyostelium* and similar cells is controlled by an excitable network that encompasses components of the actin cytoskeleton and associated signaling pathways.[50] The basic conceptual element of the proposed scheme consists of a double feedback loop between signaling molecules that act as activators and inhibitors of cell motility (**Fig. 3A**). Despite the fact that the molecular identity of the primary activator and inhibitor and their interactions have not been fully established in *Dictyostelium*, it has been assumed that the final "readout" of the networks' activity is the local polymerization of actin.[50] Furthermore, it has become increasingly clear that not only one, but multiple feedback loops are involved in this excitable regulatory mechanism, involving global and local, as well as activating and inhibitory interactions.[50] One such loop regulates the balance between important signaling phospholipids, phosphatidylinositol [4,5] bis-phosphate (PIP2) and phosphatidylinositol [3,4,5] trisphosphate (PIP3), that are interconverted by PI3K kinase and PTEN phosphatase.[51] The zones labeled with PIP3 and PTEN probes are mutually exclusive and together they cover the entire surface of the plasma membrane in *Dictyostelium* cells.[51] It has been proposed that PIP3 and PTEN constitute an autonomous oscillatory system based on their mutual cross-inhibition.[52] This model belongs to a class of mass-conserved reaction-diffusion models where negative regulation of a component in a reaction system can be traced back to its limited supply.[53]

We propose that the regulation of spatiotemporal dynamics of Rac1 activity is governed by a similar mechanism (**Fig. 3B**). However, instead of two enzymes that conversely influence the local concentration of PIP3, the central role is assumed by a pair of effectors, DGAP1/cortexillin and Scar/WAVE complex, that compete for a common pool of active Rac1 (**Fig. 3C**). Under conditions where the total amount of active Rac1 in a cell is limited, and can be adjusted e.g., by the basic GEF-GAP-GDI regulatory mechanism, the mutual inhibition of the two effectors is automatically warranted. This condition is fulfilled in mammalian cells where less than 10% of the major cellular Rho GTPases, including Rac1, are located at the membrane in their GTP-bound state, while the majority is sequestered in a GDI-bound form in the cytoplasm.[54,55] It remains to be seen whether other interactions between the two effector complexes in *Dictyostelium* contribute to the overall feedback network.

In conclusion, we have obtained evidence through the use of specific fluorescently labeled probes that activated Rac1 GTPases are involved in regulation of actin cytoskeleton dynamics both at the front and the back of migrating *Dictyostelium* cells. Due to its dual role, Rac1 might be one of the key signaling proteins that regulate the sustained morphological oscillations typical for randomly migrating *Dictyostelium* cells.[6] Based on these findings we hypothesize that Rac1 effectors can downregulate each other by competing for a limited pool of active Rac1. It is therefore tempting to speculate that similar mechanisms may play a general role in mutual regulation of signaling pathways downstream of Rho GTPases in various actin-based processes.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.


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